IOWA STATE UNIVERSITY
Digital Repository

Volume 1 | Issue 3 Article 8

1939

Therapeutic Trends

H. D. Bergman
Iowa State College

Therapeutic Trends

H. D. BERGMAN

Department of Veterinary Physiology and Pharmacology
Iowa State College

PROBLEMS of therapeutics in veterinary medicine are much more complex than those of human medicine. The veterinarian deals with various species of animals, each with its peculiar diseases and varied reactions to standard drugs. Plans of medication are often difficult problems, especially where a considerable number or where large or refractory animals are involved. Yet, veterinary therapeutics has made tremendous progress within very recent years both as to methods and products, the latter differing but very little from those of general application in human medicine.

Outstanding are the advances in specific anthelmintic therapy for various species of parasites and in parenteral methods utilizing certain sodium and calcium salts to support the potential alkalinity of the body fluids or correct quantitative calcium deficiencies. Dextrose is utilized as an antiketogenic agent in ketosis as are reducing agents such as sodium nitrate, sodium thiosulphate, and methylene blue in certain intoxications and metallic poisonings. Foreign proteins, cellular products, and various other types of colloidal preparations are used parenterally to promote allergic reactions with resultant stimulation of natural body defense such as leucocytosis. Even acids, such as diluted hydrochloric acid, are used intravenously for a similar purpose. The intravenous use of certain dyes has come into therapeutic prominence, their value lying both in their bactericidal or bacteriostatic properties and also their colloidal character. More recently, synthetic chemicals such as sulfanilamide and sulfapyridine with specific bacteriostatic properties have revolutionized certain medical practices.

Fortunately, secret formula preparations no longer have a place in professional medicine. The policy of the ethical veterinary medical supply houses of indicating plainly the composition of their various pharmaceutical preparations is a most progressive step. Proprietary preparations as a class now occupy an important place in both human and veterinary therapeutics because they are no longer proprietary in the light of being of secret composition; protection to the manufacturer is afforded by patent or copyright. Most of the inclusions in the publication, "New and Nonofficial Remedies", of the Council on Pharmacy and Chemistry of the American Medical Association are proprietary in character but are approved for use by the medical profession. Veterinary medicine uses widely of N.N.R. approved preparations, the majority of which are products of organic synthetic chemistry.

Synthetic Chemicals

If one doubts the trend toward an increasing use of synthetic chemicals in the treatment of disease, he need but study the United States Pharmacopoeia, Eleventh Revision, which became official June 1, 1936. Of 58 new products added to the eleventh revision, 28 are organic chemicals mostly synthetic in origin. Even the synthetic or artificial forms of the two old medicinal stand-bys, camphor and menthol, are now official drugs. Of the 119 articles dropped from the U. S. P. XI, only 16 are organic chemicals and these mostly alkaloidal salts; the rest are chiefly fluid extracts, liquors, pills, syrups, tinctures, and ointments. It is evident that the medical professions are becoming synthetic-chemically minded to the detriment of the old Galenicals.

A tendency in modern synthetic chemistry is to isolate the active principles

from natural drugs, determine their chemical structure and then prepare them synthetically, often more cheaply and sometimes with improvement over the natural product.

Witness the development of the many artificial synthetic local anesthetics as improvements over the natural alkaloid, cocaine. On the premise that all parts of the complex, rather toxic and habit-forming cocaine molecule were not essential for anesthesia, the chemical structure of cocaine was determined and there were found to be three important groups of atoms or rings; (1) a group of atoms, or ring, common to a series of alkaloids such as nicotine, quite toxic and not essential to local anesthesia; (2) a ring also occurring in certain toxic alkaloids such as coniine and relatively unimportant in the anesthetic effect; (3) a group of atoms, the "benzoyl" group, relatively non-toxic and particularly important for anesthesia. By chemical manipulation of these groups, it was found possible to produce artificially a base analagous to cocaine, possessing most of the anesthetic properties of cocaine and losing approximately two-thirds of its toxic properties. Such was the development of novocaine or procaine, one of our most valuable synthetic and relatively non-toxic local anesthetics.

Narcotics

More recently in the field of narcotic drugs, synthetic chemistry has created new therapeutic products of tremendous value. Among the newer synthetic chemical agents with anodyne, hypnotic, or actually anesthetic properties are the barbital (diethylbarbituric acid) derivatives. Barbital was introduced into medicine as veronal in 1904 but neither it nor its derivatives has been much used in veterinary medicine until comparatively recently when several new barbital derivatives, developed by chemists attempting to improve upon barbital, have been found to have an important place in small animal medicine.

The official barbital compounds in U. S. P. XI are as follows: Barbital (diethylbarbituric acid), soluble barbital (barbital sodium), phenobarbital (luminal), soluble phenobarbital (luminal sodium), elixir barbital and elixir phenobarbital. Other unofficial but highly valuable barbituric acid derivatives in veterinary medicine are pentobarbital sodium (nembutal), amytal, amytal sodium, pentothal sodium, a new sulfur-containing barbiturate to produce short anesthesia by intravenous method, and others. Each has its particular field of usefulness; for example, in luminal, nerve sedative properties have been especially developed, in amytal, sleep-producing or hypnotic properties are more evident and in nembutal, anesthetic properties predominate. Taking barbital, known to medicine as veronal for many years and little used, synthetic chemistry has produced from this base a large number of derivative compounds each differing somewhat as to properties from its relatives and all of value to medicine.

Hormones and Vitamins

Synthesis of the hormones and vitamins is now commanding great interest in the field of synthetic chemistry. Examples of the former that have been prepared synthetically are thyroxine and epinephrine and of the latter, vitamin A and three chemical entities of the vitamin B complex, i.e. vitamin B_1 (thiamin chloride), the P-P factor (nicotinic acid) and B_2 (riboflavin). Synthetic ascorbic acid appears to represent the most active form of vitamin C. There would appear to be no limit to the field of synthetic chemistry.

Chemotherapy

In retrospect, the years 1936, 37, 38, will be noted for the revived interest in "chemotherapy", a term coined and restricted in use by Paul Ehrlich, a German scientist (1854-1915), to the parasiticidal or bactericidal treatment of infections by the use of specific chemical agents. He worked systematically to extend this field by synthetic methods directed toward the development of chemical substances, which, through selective protoplasmic affinity show a relatively high toxicity for the infective organism and low toxicity for the host. The most

effective chemotherapeutic agents discovered by Erhlich and independent workers belong to approximately four groups, i.e. benzidine dyes, basic triphenylamine dyes, arsenic compounds and antimony and bismuth compounds.

Outstanding among the arsenic compounds developed by Erhlich is arsphenamine (salvarsan, 606) and its derivatives which show a high selectivity against the causative organism of syphilis and a relatively low toxicity for the host. Although clinical experience has shown some advance in the chemotherapy of protozoan diseases, the record until very recently against bacterial diseases has indicated practically a complete failure. It appears that the more highly developed the pathogenic organism, the more points of attack it offers to the action of chemotherapeutic agents. Little has been known of the treatment of bacterial infections due to cocci and bacilli, types of infective agents occupying the lowest level in the scale of microorganisms. The spirochetes, and still more so organisms which belong to the protozoa are more readily attacked by chemical substances; hence, best clinical results have been obtained in spirochetal diseases such as syphilis, and especially in protozoan diseases. Therefore, the recently introduced chemical, sulfanilamide, and its apparently successful employment in the treatment of diseases caused by diverse pathogenic bacteria constitutes the greatest advance in chemotherapy since the discovery of salvarsan (arsphenamine).

Sulfanilamide and Sulfapyridine

The mechanism of the curative action of sulfanilamide has been much discussed. It does not destroy the micro-organisms; however, bacteriostatic effects have been demonstrated both "in vitro" and "in vivo". The suggested role of neutralization of bacterial toxins remains to be established. Potentiation by the drug of the action of antiserum has been demonstrated both in culture and in infected animals. Antiserum and sulfanilamide are synergists. A striking aspect of treatment appears to be a depression of the invasive properties of the micro-organism causing the disease. This effect is definite within a few hours in the case of bacteria circulating in tissue fluids or in newly invaded tissues. However, in tissue already broken down effectiveness is much impaired or may be lost.

It is not known whether the debris itself in the broken-down tissue protects the organisms or whether the drug cannot penetrate sufficiently into the tissue when debris is present. This may explain its greater effectiveness in acute rather than chronic conditions. In any event, the organisms are not destroyed by the drug but rather are so inhibited as to be more readily destroyed by the natural body defenses. While much needs to be done to determine the exact fields of usefulness for sulfanilamide in veterinary therapeutics and for the time being its use must be more or less empirical, there is no doubt that it represents one of the greatest medical discoveries of modern times. It is one of the first of a group of chemotherapeutic agents for bacterial infections which may revolutionize the treatment of diseases.

A more recent development than sulfanilamide in the field of chemotherapy is a chemical called sulfapyridine. While sulfanilamide has been reported as effective in certain types of pneumonia, sulfapyridine appears to be much more effective for many types of pneumococcic infection. This product, recently approved by the Federal Food and Drug Administration for distribution and use by the medical professions, possesses much of the action of sulfanilamide against certain groups of bacteria. In addition, it is especially effective against those organisms etiologically related to the dread disease, pneumonia. Such clinical data at present available on this recently introduced drug are so definitely encouraging as to indicate it will assume proportions in the treatment of pneumonias comparable to sulfanilamide in certain other types of infection.

Neurohormones

The above term is applied to diffusible chemical substances formed at nerve ter-

minations upon stimulation of a nerve. The discovery that the final transmission of nerve impulses is by means of chemical substances released at the nerve endings marks one of the most important scientific discoveries of modern times and is of direct therapeutic significance. This is shown by the fact that the 1936 Nobel Prize in medicine and physiology was awarded jointly to Sir Henry Dale, director of the British National Institute of Medical Research, London, and Dr. Otto Loewi of the University of Graz, Austria, for their research and discoveries in this field. The most definite research involving the neurohormones has been done on the autonomic nervous system where the chemical or humoral transmitter of parasympathetic stimuli has been shown to be acetylcholine and the transmitter of sympathetic stimuli to be an adrenaline-like substance called sympathin, not yet isolated.

The demonstrated relationship of acetylcholine to the transmission of parasympathetic nerve impulses suggested the possibility of the application of it or derivatives therapeutically. Such derivatives have been developed by various syntheses and great usefulness is foreseen. Two products, acetyl beta methylcholine chloride (Mecholyl) for human use and carbamylcholine chloride (Lentin) for veterinary use, have recently come into prominence. Developed synthetically, following physiological research on the functioning of nerve endings, the product Lentin has apparently many of the actions of the group of alkaloids pilocarpine, eserine and arecoline, and possibly some special actions not possessed by them. Here again are products of synthetic chemistry which may have an important place in therapeutics.

In conclusion, let it be said that while we hear much of disease prevention and of the technics of preventive medicine which of course are vitally essential and represent the ideal situation, curative medicine and its technics can by no means be relegated to secondary consideration. Tremendous progress is being made in this field due largely to synthetic chemical methods, and the future possibilities in both human and veterinary medicine are indeed great.

A Peracute Complication of Distemper

On February 27, 1939, Mr. Kark of Blue Earth, Minnesota presented at the small animal clinic a one-year old Great Dane (male) with a severe case of canine distemper. The history revealed that the dog had begun to show symptoms of depression, loss of appetite, nasal catarrh, and diarrhea about three days previously. The prognosis was very unfavorable, and the dog was given Neoprontosil to no avail. The next day, February 28; the dog died. The course of the affection was thus about five days.

The dog was given the regular post mortem examination, and the pathological changes were acute bilateral pneumonia with focal necrosis, acute right cardiac dilatation with cardiac cloudy swelling, general serous lymphadenitis, acute catarrhal gastro-enteritis, hepatic and renal cloudy swelling.

Two other yearlings from the same kennels and litter died with the same rapid course of distemper; but they were not brought to the clinic, nor were they given a post mortem examination.

In the same kennel a three-year old bitch and her seven, eight weeks old pups, began to show symptoms of depression followed by a diarrhea on February 18, and by February 27, the bitch and pups had died from apparently a severe septicemia complicating distemper.

The course of the disease was five days in the bitch; and on post mortem examination of the bitch and several of the pups, which were brought in to the diagnostic laboratory, they showed, in addition to the lesions mentioned above, a severe hemmorhagic gastro-enteritis and focal necrosis of the liver.—**Melvin Hofstad**